REMARKS

Applicants' representatives thank Examiner Bridget Bunner, Primary Examiner Elizabeth Kemmerer, Supervisory Examiners Yvonne Eyler and Gary Kunz for the courtesy extended during the interview on April 14, 2003. The amendments and remarks herein are made in accordance with our discussion during the interview.

Status of the claims

Upon entry of this amendment, claims 26-28, 31-41, 44, 45, 48-61, 70-81, 83-86, 95-107, 116-125, 128, 132, 134-143, 146, 150, 152-161, 164, 168, 170-179, 182, 186, 188-196, 205-213, 215, 225-231, 247-251, 260-273, 282-290, 293, 297, 299-307, 310, 314, 316-324, 333-341, 343, 352-359, 362, 366, 370, 378, 382, 386, 390, 410, 414, 424-430 will be pending. Cumulatively, Applicants have cancelled claims 1-25, 29, 30, 42, 43, 46, 47, 62-69, 82, 87-94, 108-115, 126, 127, 129-131, 133, 144, 145, 147-149, 151, 162, 163, 165-167, 169, 180, 181, 183-185, 187, 197-204, 214, 216-224, 232-246, 252-259, 274-281, 291, 292, 294-296, 298, 308, 309, 311-313, 315, 325-332, 342, 344-351, 360, 361, 363-365, 367-369, 371-377, 379-381, 383-385, 387-389, 391-409, 411-413 and 415-423 without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of the claims cancelled herein in one or more continuing applications.

The Examiner has indicated that claims 26-28, 31-34, 36-38, 124, 125, 134-137, 139-143, 152-155 and 157-159 are allowable (see Paper No. 17, page 11). As regards the allowable claims, Applicants wish to point out to the Examiner that a minor amendment has been made to each of claims 125 and 143.

Amendments to the claims

Amendments to the claims have been made in accordance with the discussion during the interview on April 14, 2003. For convenience, in the present response, Applicants will refer the Examiner to disclosure in the specification by referencing the appropriate paragraph numbers of the Substitute Specification that was submitted on May 3, 2002.

In claims 39, 160, 178, 290 and 307, the words "modulates leukocyte" have been replaced with the words "stimulates lymphocyte." In claims 128, 132, 146, 150, 164, 168,

182, 186, 293, 297, 310, 314, 362, 366, 370, 378, 382, 386, 390, 410 and 414, the word "leukocyte" has been replaced with the word "lymphocyte." Support for these amendments may be found, for example, in the specification in paragraphs [0040], [0153], [0156], [0622] and Examples 6 and 7.

Claims 57, 78, 103, 196, 213, 247, 268, 324 and 341 have been amended to replace the phrase "modulates leukocyte proliferation, differentiation or survival" with the phrase "can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2." Support for these amendments may be found, for example, in the specification in paragraphs [0331], [0342] – [0491] and Example 9.

The dependency of claims 35, 53, 74, 99, 120, 138, 156, 174, 192, 209, 228, 264, 286, 303, 320, 337, 356 has been amended such that these claims now depend from claims reciting radiolabeled forms of the Neutrokine-alpha protein. Support for these amendments may be found, for example, in the specification in paragraphs [0539], [0448], [0531], [0542]-[0545], [0714], [0716] and [0783].

In claims 125 and 143, the word "protein" has been amended to "polypeptide."

Applicants have reinstated former claim 214 as new claim 430 and corrected the dependency of claim 225 to depend on claim 430, thereby re-establishing antecedent basis for the term "heterologous sequence" in claim 225.

The dependency of claim 343 has been amended to depend from claim 341, rather than cancelled claim 242.

Claims 378 and 382 have been amended to depend from claims 124 and 142, respectively.

No new matter has been added by way of amendment. Applicants respectfully request that these amendments be entered.

Information Disclosure Statement:

The Examiner has not considered the references cited in the First Supplemental Information Disclosure Statement submitted on May 3, 2003 in the present application because she contends the First Supplemental Information Disclosure Statement did not comply with 37 C.F.R §1.98(a)(2). Applicants disagree and point out to the Examiner that the First Supplemental Information Disclosure Statement referred the Examiner's attention to parent application Number 09/005,874 for copies of the references in accordance with the provisions of 37 C.F.R §1.98(d). References B1-B5 were cited as references C1-C5 on

the revised Form PTO/SB/08 submitted in the 09/005,874 application on January 25, 2002. Additionally copies of references B1-B4 were cited as references B1, B2, B4 and B5 on the revised Form PTO/SB/08 submitted in the 09/255,794 application on July 8, 2002. Applicants respectfully request reconsideration of these references.

In a telephone conversation with Examiner Bunner on June 4, 2003, Applicants indicated references B1-B5 had been cited in other applications related to the present application. The table below indicates three related applications in which these references have been cited to the United States Patent and Trademark Office. A courtesy copy of reference B5 is being provided with this response because the reference is the only non patent-related publication in references B1-B5 and because the reference is small and easily transmitted by facsimile. If the Examiner is unable to locate the copies of the remaining references, please let Applicants know by telephone and Applicants will arrange for new copies of the references to be submitted.

Related Application No.	Reference Identifiers in Related Application	Cited to Examiner on Form PTO-SB/08 dated	Examiner initialed and returned copy of PTO-SB/08 to Applicants with Office Action (Paper No and date of Office Action and Examiner's name)	Copies of references submitted / Reference to case under 37 CFR § 1.98(d)
09/005,874	C1-C5	January 25, 2002	Paper No. 23 April 23, 2002 Sarada Prasad	Yes
09/255,794	B1, B2*, B4, B5 = B1-B4 of present application	July 8, 2002	Paper No. 25 October 1, 2002 Bridget Bunner	Yes
09/588,947, now US Patent 6,562,579	B1-B5	March 26, 2002	Paper No 13 October 9, 2002 Sarada Prasad	Referred Examiner to 09/005,874 under 37 CFR § 1.98(d)

*B2 is cited by publication number in '794 application where as the same document, B2 in present application, was cited by its application serial number

Claim Objections

Claims 215 and 343 are objected to for depending from cancelled claims. Upon entry of the present amendment, claim 343 will depend from a pending claim.

With respect to claim 215—claim 215 was first presented on August 14, 2001 depending from claim 214. However, in the Clean Version Of The Entire Set Of Pending Claims Under 37 C.F.R. § 1.121(c)(3) provided to the Examiner by Applicants on May 3,

2002 claim 215 depended on claim 213, not claim 214. This dependency was never formally amended to claim 213. According to the rules, however, a submission of a clean version of the entire set of pending claims submitted in a single amendment paper under 37 C.F.R. § 1.121(c)(3), shall be construed as directing the cancellation of all previous versions of any pending claims. Applicants were in error by not submitting a marked up version of that amendment in their Response and Amendment filed May 3, 2003. This omission of the submission of the marked up version of claim 215 on May 3, 2002 occurred by accident and without deceptive intent. Applicants have therefore not amended claim 215 herein, because the claim as presented on May 3, 2002 did not depend from a cancelled claim. Furthermore, upon discovery of this accidental omission of a marked up version of an amended claim, Applicants have carefully reviewed the Clean Version of the Entire Set of Pending Claims submitted on May 3, 2002, and have not found any other errors or omissions. Applicants apologize for their error.

Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph

B. Enablement

Claims 35, 39-41, 44, 45, 48-81, 83-123, 126-133, 138, 144-151, 156, 160-213, 215-223, 225-238, 240-341 and 343-429 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

Specifically, the Examiner states that

> [t]he specification does not teach any functional or structural characteristics of fragments, derivatives, or variants of the neutrokine-alpha polypeptide of SEQ ID NO:2 other than polypeptides comprising amino acids 73-285 or amino acids 134-285 of SEQ ID NO:2, other than polypeptides comprising amino acids 73-285 or amino acids 134-285 of SEQ ID NO:2 The specification does not teach any methods or working examples that indicate polypeptide variants that do not contain amino acids 134-285 of SEQ ID NO:2 have any function." (Paper No. 17, page 5).

In accordance with the discussion during the interview on April 14, 2003, Applicants have amended claims 57, 78, 103, 196, 213, 247, 268, 324 and 341 to replace the phrase "modulates leukocyte proliferation, differentiation or survival" with the phrase

"can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2." Applicants believe that in view of the discussion above and at the interview of April 14, 2003, and in view of the amendments made herein, this rejection as it applies to these claims and claims dependent therefrom, has been obviated or overcome. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. §112, as it applies to claims 57, 78, 103, 196, 213, 247, 268, 324 and 341 and any claims dependent therefrom, be reconsidered and withdrawn.

The Examiner further states that,

> Applicants has amended the originally filed claims and added claims to recite the limitation that the neutrokine-alpha protein "modulates leukocyte proliferation, differentiation or survival". However...the specification teaches that neutrokine-alpha induces B cell proliferation and differentiation and displays a clear B cell tropism in both its receptor distribution and biological activity (pg 327-329). The specification does not teach that neutrokine-alpha increases/decreases the proliferation, differentiation, or survival of all possible leukocyte cells....The specification of the instant application clearly indicates that [binding of] biotinylated neutrokine-alpha is undetectable on T cells, monocytes, NK cells, and granulocytes and that neutrokine alpha stimulates the proliferation and differentiation of B cells (pg. 327, [0846] through pg 329). Therefore, one skilled in the art would not be able to predict that neutrokine-alpha would be able to increase or decrease the proliferation or differentiation of any leukocyte cells, other than B cells. The specification also does not teach that neutrokine-alpha affects the survival of any leukocytes, including B cells. (Paper No. 17, pp. 6-7)

Preliminarily, Applicants have amended claims 39, 128, 132, 146, 150, 160, 164, 168, 178, 182, 186, 290, 293, 297, 307, 310, 314, 362, 366, 370, 378, 382, 386, 390, 410 and 414 to replace the term "leukocyte" with "lymphocyte." Additionally, Applicants have replaced the term "modulates" with "stimulates" in claims 39, 160, 178, 290, and 307 Applicants note for the record, as noted in the interview summary dated April 14, 2003, the claiming of neutrokine-alpha polypeptides that stimulate lymphocyte proliferation, differentiation or survival does not preclude the claimed proteins having other activities such as, for example, the ability to decrease lymphocyte proliferation, differentiation, or survival. In light of these amendments, Applicants will only address the Examiner's concerns insofar as the rejection applies to the claimed proteins' ability to stimulate lymphocyte proliferation, differentiation or survival.

Applicants point out that the specification discloses that Neutrokine-alpha promotes lymphocyte proliferation, differentiation, and survival (see e.g., paragraphs [0005], [0023], [0153], [0154] and [0156] and Examples 6 and 7, particularly paragraphs [0850] and [0851]). These statements are presumptively accurate (See, M.P.E.P., 8th edition, section 2164.04, bottom right of page 2100-178), and have been corroborated by the use of post filing date data. Applicants assert that the use of post filing date data to corroborate the enablement of a claim is in accordance with relevant case law. The Federal Circuit held in *In re Brana*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." 51 F. 3d. 1560, 1567 at n19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id., citing In re Marzocchi*, 439 F2d. 220 at 224 n.4. Indeed, Applicants assertions that Neutrokine-alpha stimulates lymphocyte proliferation, differentiation and survival have been substantiated by post filing-date data. In the following discussion, the literature names of Neutrokine-alpha including "BAFF" and "BLyS" will be used. Emphases are added in the following four paragraphs.

MacKay et al.[1] (cited as reference A57 on the PTO/SB-08 submitted August 14, 2001) state that "[a]t equal cell concentration, splenocytes isolated from BAFF-Tg [BAFF-transgenic] mice *survived* longer in culture when compared with control splenocytes" (p. 1703, left column); "BAFF is a powerful cytokine affecting B cells, and *has consequences for T cell* and dendritic cell status." (p. 1706, top of right column); "The presence of large germinal centers in secondary lymphoid organs of BAFF-Tg mice, *higher total T cell numbers* in the spleen and MLN [mesenteric lymph node] as well as increased proportion of both CD4 and CD8 effector T cells in the periphery, and the quality of RF isotypes strongly suggest the active participation of T cells in the immune reactions triggered in BAFF-Tg mice." (p. 1708, lower left column).

Parry et al.[2], (cited as reference A61 on the PTO/SB/08 submitted August 14, 2001) characterize Neutrokine-alpha as a "growth factor that *promotes B cell proliferation and differentiation*" (p. 401 right column, top).

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[1] MacKay et al., Mice Transgenic for BAFF Develop Lymphocytic Disorders Along with Autoimmune Manifestations, *The Journal of Experimental Medicine* (1999) 190:1697-1710.
[2] Do et al., Attenuation of Apoptosis Underlies B Lymphocyte Stimulator Enhancement of Humoral Immune Response, *The Journal of Experimental Medicin* ., (2000) 192:953-964.

Do et al.[3], (cited as reference A50 on the PTO/SB/08 submitted August 14, 2001) teach that "[a]ttenuation of apoptosis by BLyS is not restricted to B cells after activation by antigen or CD40L, as BLyS also prolongs the *survival* of high density B cells after antigen challenge in vivo (data not shown) and naïve resting B cells in vitro (Figure 7)." (p. 962 right column, middle).

Huard et al.[4], (provided herewith as Exhibit A) conclude that "it can be said that BAFF regulates both B and T cell activation, with an overall enhancement of *proliferation* and *effector responses* (Ig secretion for B cells and cytokine secretion for T cells)." (p. 6230, right column, middle). The induction of cytokine or immunoglobulin secretion is an indication the T or B cells have undergone a differentiation step.

Taken together these results confirm Applicants assertions that Neutrokine-alpha is able to stimulate lymphocyte proliferation, differentiation, or survival. Applicants believe that in view of the discussion above and at the interview of April 14, 2003, and in view of the amendments made herein, this rejection as it applies to claims 39, 128, 132, 146, 150, 160, 164, 168, 178, 182, 186, 290, 293, 297, 307, 310, 314, 362, 366, 370, 378, 382, 386, 390, 410 and 414 and any claims dependent therefrom has been obviated or overcome. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

The Examiner also contends that, "the specification does not teach that neutrokine-alpha is cytotoxic to neutrokine-alpha receptor bearing cells." (Paper No. 17, page 7) Though Applicants disagree, in the interest of facilitating prosecution, Applicants have amended the dependency of claims 35, 53, 74, 99, 120, 138, 156, 174, 192, 209, 228, 264, 286, 303, 320, 337, 356 to depend from claims reciting radiolabeled forms of the Neutrokine-alpha protein. Applicants believe that in view of the discussion above and at the interview of April 14, 2003, and in view of the amendments made herein, this rejection as it applies to claims 35, 53, 74, 99, 120, 138, 156, 174, 192, 209, 228, 264, 266, 303, 320, 337, 356 has been obviated or overcome. Accordingly, Applicants respectfully

[3] Parry et al., Pharmac kinetics and Immunological Effects of Exogenously administered Recombinant Human B Lymphocyte Stimulator (BLyS) in Mice, The Journal of Pharmacology and Experimental Therapies Therapeutics, (2001) 296:396-404.
[4] Huard et al., T cell costimulation by the TNF Ligand BAFF, *The Journal of Immunology*. (2001) 167:6225-6331.

request that this rejection under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

The Examiner also contends that "the specification of the instant application does not teach any methods or working examples that generate a neutrokine-alpha protein multimer. There is no guidance in the specification teaching one skilled in the art how to create a neutrokine-alpha multimer and undue experimentation would be required of the skilled artisan to do so." (Paper No. 17, paragraph spanning pp. 7-8).

Applicants respectfully disagree. Neutrokine-alpha in its native state, like other TNF ligand family members, forms multimers, and in particular, is known to form trimers. This is indicated in the specification in paragraph [0005]. Furthermore, standard methods of expression and purification of Neutrokine-alpha as known in the art and/or described in the specification, at for example, paragraphs [0159]- [0196], Examples 1-3, and Example 6, would routinely result in the production of a multimeric Neutrokine-alpha protein. In the Kanakaraj et al. reference, cited as reference A54 with the Information Disclosure Statement submitted on August 14, 2001, Neutrokine-alpha was expressed in insect cells and was purified according to standard purification protocols, much like those described in Examples 3 and 6. The resulting Neutrokine-alpha polypeptide obtained was a multimeric, specifically a homotrimeric, form of Neutrokine-alpha (see page 26 of Kanakaraj et al).

Furthermore, multimeric forms of Neutrokine-alpha proteins may also be obtained through recombinant or chemical methods known in the art and/or as described in the specification, at for example, paragraphs [0197]-[0205]. As one example, it has long been known that production of a protein as an Fc fusion protein imparts a dimeric structure to the fusion protein. Thus, recombinant methods and/or chemical could be used to make Neutrokine-alpha multimers. Thus, Applicants submit it would not require undue experimentation for one of skill in the art to make and use a Neutrokine-alpha multimer.

Applicants believe that in view of the discussion above and at the interview of April 14, 2003 this rejection has been obviated or overcome. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

B. Written Description

The Examiner also rejects claims 57-60, 62-81, 83, 87-104, 108-123, 126-133, 138, 144-151, 156, 160-213, 215-223, 225-232, 234-238, 240-272, 274, 276-341 and 343-429 for alleged lack of written description. In view of the discussion above and at the interview of April 14, 2003, and in view of the amendments made herein, Applicants believe that this rejection has been obviated or overcome. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

C. Conclusion of Applicants' Response to Rejections under 35 U.S.C. §112, first paragraph

Applicants believe that the entirety of the Examiner's rejection of claims under 35 U.S.C. §112, first paragraph, for alleged lack of enablement and written description have been addressed and obviated or overcome. Accordingly, Applicants respectfully request that the Examiner's rejection under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claims 39-41, 44-45, 48-81, 83-123, 126-127, 130-131, 144, 145, 148, 149, 160-213, 215-223, 247-272, 274, 275, 278, 279, 290-342, and 343-429 are rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In accordance with the discussion during the interview of April 14, 2003, the word "modulates" in claims 39, 160, 178, 290 and 307 has been amended to "stimulates." Additionally, and also in accordance with the discussion during the interview of April 14, 2003, the term "modulates" was removed from claims 57, 78, 103, 196, 213, 247, 268, 324, 341 by the amendment (made herein) that replaces the phrase "modulates leukocyte proliferation, differentiation or survival" with the phrase "can be used to generate or select for an antibody that specifically binds the polypeptide of SEQ ID NO:2." The remaining claims rejected under 35 U.S.C. §112, second paragraph, either depend from these amended claims or were cancelled.

Applicants believe that in view of the discussion above and at the interview of April 14, 2003, and in view of the amendments made herein, this rejection has been

obviated or overcome. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. §112 be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present Amendment be entered and made of record in the present application.

In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance. An early Notice of Allowance is earnestly solicited. If in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425.

Respectfully submitted,

Date: June 4, 2003

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